6

ITEM 16.
DEBARMENT CERTIFICATION

Warner-Lambert Company certifies that it is not debarred, and to the best of its knowledge Warner-Lambert Company did not and will not use in any capacity the services of any person debarred under Section 306(a) or 306(b) of the Federal Food, Drug, and Cosmetic Act in connection with this application.

RECORD OF TELEPHONE CONVERSATION/MEETING	**Date:** May 17, 1999
Date: Thursday, May 13, 1999 Location: Parklawn 1456 Time: 2:00-3:00PM FDA Attendees: Dr. Orloff David Hoberman Margaret Simoneau Parke-Davis Attendees: Linda Shurzinske Dave Pyne Theresa Stern Jeff Koup	**IND/NDA#:**20-702/S-018 **Telecon/Meeting initiated by:** Applicant/Sponsor **By:** Telephone **Product Name:** Lipitor (atorvastatin) **Firm Name:** Parke-Davis

1. Meeting Objective
This was a telephone conference requested by the sponsor for clarification of the May 6 fax sent to Parke-Davis by the Agency.

2. Discussion and Decisions
Discussion involved the statistical submission of Lipitor efficacy supplement 18 which was submitted March 3, 1999. At the Agency filing meeting on April 22, 1999, David Hoberman requested the sponsor submit the statistical information in a particular format. The request was faxed to the sponsor on May 6, 1999 (see enclosure 1). Also included in the discussion was a Parke-Davis fax dated May 13, 1999 (enclosure 2).

A. A cumulated distribution curve not a histogram was desired.
B. Weighted information- to get met analysis for each dose; give four confidence intervals.
C. Want to see the plots with respect to stratification and with respect to titration studies (want unequivocal dosing).

David Hoberman provided the sponsor his direct phone number if there any further questions or clarifications to the request.

cc: NDA 20-702/S-18
DivFile

/S/

Phone: 734-622-5225

NDA 20-702/S-018

Parke-Davis Pharmaceutical Research
Warner-Lambert Export, Limited
2800 Plymouth Road
Ann Arbor, MI 48105

Attention: Byron Scott, R.Ph.
Director, Worldwide Regulatory Affairs

Dear Mr. Scott:

We acknowledge receipt of your supplemental application for the following:

Name of Drug:	Lipitor® (atorvastatin calcium) Tablets
NDA Number:	20-702
Supplement Number:	S-018
Date of Supplement:	March 03, 1999
Date of Receipt:	March 04, 1999

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on May 03, 1999, in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Attention: Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

/S/

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine
Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Pharmaceutical Research
2800 Plymouth Road Phone: (734) 622-7000
Ann Arbor, MI
48105

PARKE-DAVIS

November 17, 1999

NDA 20-702
Ref. No. 101
Lipitor® (atorvastatin calcium) Tablets

Re. Amendment to Efficacy
Supplement – 018:
Revised Draft Labeling

Solomon Sobel, M.D.
Director
Division of Metabolism and Endocrine
Drug Products (HFD-510)
Document Control Room 14B-19
Center for Drug Evaluation and Research
Food and Drug Administration
Parklawn Building
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Sobel:

On behalf of, and as agent for Warner-Lamber Export, reference is made to our supplement (S-018), submitted March 3, 1999 (Ref. No. 83), to our approved NDA 20-702 for Lipitor® (atorvastatin calcium) Tablets. This supplement supports the use of atorvastatin to increase HDL-C in patients with primary hypercholesterolemia (hetrozygous familial) and mixed dyslipidemia (Fredrickson Type IIa and Type IIb). Reference is also made to a request made by Dr. Orloff on November 16, 1999 for additional changes in the revised draft labeling, submitted November 5, 1999 (Ref. No. 100). In response to Dr. Orloff's requests, we are hereby submitting revised draft labeling for this efficacy supplement (Attachment 1).

New text (highlighted) has been added under the CLINICAL PHARMACOLOGY, Clinical Studies section on pages 4 and 5 of the revised draft labeling. In addition, the INDICATIONS AND USAGE section on pages 7 and 8 has been modified (current labeling text is shown with strike-through, new text is highlighted). Additional wording, as requested by Dr. Orloff on November 16, 1999, has been added under WARNINGS, Skeletal Muscle and Drug Interactions on page 11 of the revised draft labeling.

Should you have any questions regarding this submission, please contact me at 734/622-5225 or send a facsimile to 734/622-3283.

Sincerely,

Jeffrey Koup, Pharm.D.
Director
Worldwide Regulatory Affairs

Desk Copy: Dr. David Orloff (HFD-510)
Ms. Margaret Simoneau (HFD-510)

JK:kb
11-17-1999\RN-101\20-702\CI-0981\Letter

Attachment

Pharmaceutical Research
2800 Plymouth Road Phone: (734) 622-7000
Ann Arbor, MI
48105

R DAVIS

NDA SUPP AMEND
SE1-018-Rh

November 5, 1999

ORIGINAL

NDA 20-702
Ref. No. 100
Lipitor® (atorvastatin calcium) Tablets

Re. Amendment to Efficacy
Supplement – 018:
Revised Draft Labeling

Solomon Sobel, M.D.
Director
Division of Metabolism and Endocrine
Drug Products (HFD-510)
Document Control Room 14B-19
Center for Drug Evaluation and Research
Food and Drug Administration
Parklawn Building
10 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Sobel:

On behalf of, and as agent for Warner-Lamber Export, reference is made to our supplement (S-018), submitted March 3, 1999 (Ref. No. 83), to our approved NDA 20-702 for Lipitor® (atorvastatin calcium) Tablets. This supplement supports the use of atorvastatin to increase HDL-C in patients with primary hypercholesterolemia (hetrozygous familial) and mixed dyslipidemia (Fredrickson Type IIa and Type IIb). Reference is also made to telephone conversations with Dr. David Orloff of your Division on November 3rd and 5th, 1999 discussing modifications to our proposed draft labeling. In response to Dr. Orloff's comments we are hereby submitting revised draft labeling for this efficacy supplement (Attachment 1).

New text (highlighted) has been added under the CLINICAL PHARMACOLOGY, Clinical Trials section on pages 4 and 5 of the revised draft labeling. In addition, the INDICATIONS AND USAGE section on pages 7 and 8 has been modified (current labeling text is shown with strike-through, new text is highlighted).

Should you have any questions regarding this submission, please contact me at 734/622-5225 or send a facsimile to 734/622-3283.

Sincerely,

Jeffrey Koup, Pharm.D.
Director
Worldwide Regulatory Affairs

Desk Copy: Dr. David Orloff (HFD-510)

JK:kb
11-05-1999\RN-100\20-702\CI-0981\Letter

Attachment

Pharmaceutical Research
2800 Plymouth Road Phone (734) 622-7000
Ann Arbor, MI
48105

PARKE-DAVIS

NDA SUPP AMEND
SE1-018-BM

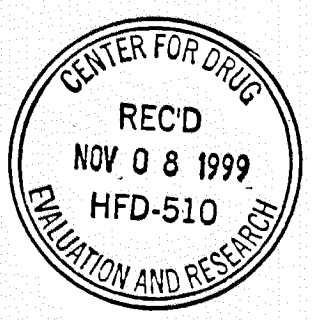
November 5, 1999

DUPLICATE

NDA 20-702
Ref. No. 099
Lipitor® (atorvastatin calcium) Tablets

Re: Request for Information

Solomon Sobel, M.D.
Director
Division of Metabolism and Endocrine
Drug Products (HFD-510)
Document Control Room 14B-19
Center for Drug Evaluation and Research
Food and Drug Administration
Parklawn Building
5600 Fishers Lane
Rockville, Maryland 20857



Dear Dr. Sobel:

On behalf of, and as agent for Warner-Lambert Export, reference is made to NDA 20-702 for Lipitor® (atorvastatin calcium) Tablets and to our efficacy supplement –018 submitted on March 3, 1999 (Ref. No. 083). Reference is also made to a telephone request made by Dr. David Orloff of your Division on October 18, 1999, for tables summarizing observed changes in plasma lipids for the database used to support our efficacy supplement.

As in the sNDA submission (RR-Memo 720-04224), data were summarized from 24 atorvastatin studies that had been completed as of July 8, 1998, including only patients with Fredrickson types IIa and IIb hyperlipoproteinemia. Baseline values corresponded to the baseline defined in the individual studies. The percent change from baseline was computed at the first or only time point used for analysis in the individual studies. Patients were summarized in the dose group that corresponded to the placebo or the first dose of atorvastatin they received in the study.

In Table 1 (Attachment 1), the mean baseline, the median, the 25th percentile, and the 75th percentile of the percent changes from baseline are provided for the placebo and for each dose of atorvastatin. This table includes summary information for HDL-C, LDL-C, total cholesterol, and triglycerides.

Table 2 (Attachment 2), contains the adjusted mean percent change from baseline in HDL-C, LDL-C, total cholesterol, and triglycerides. The adjusted means and standard errors are based on an analysis of the covariance model that includes the effects due to the study, treatment, and baseline value. Data from patients who received pravastatin 20 mg and simvastatin 10 mg were also included in the model in order to be consistent with the approach used for the sNDA.

Should you have any questions regarding this submission, please contact me at 734/622-5225 or send a facsimile to 734/622-3283.

Sincerely,

Jeffrey R. Koup, Pharm.D.
Director
Worldwide Regulatory Affairs

JK:kb
11-05-1999\RN-099\20-702\CI-0981\Letter

Attachments

PARKE-DAVIS

WORLDWIDE REGULATORY AFFAIRS
Sending Fax Number: (734) 622-CA

Pharmaceutical Research Division
Warner-Lambert Company
2800 Plymouth Road
Ann Arbor, Michigan 48105
USA

If there is a problem with the transmission please call:(734) 622-

TO: Ms. Margaret Simoneau, Project Manager

FAX #: 301-443-9282

FROM: Dr. Cheryl Anderson CA

DATE: October 25, 1999

Re: NDA 20-702/s-018
Lipitor (atorvastatin)

On October 18, 1999, Dr. David Orloff, Medical Officer, contacted Dr. Jeff Koup. Dr. Orloff requested tabular presentations of mean, median, 25th percentile and 75th percentile changes from baseline in total cholesterol, HDL, LDL and triglycerides, for the integreated database for all dose groups included in sNDA – 018. Reference is also made to teleconference held on October 21, 1999 between Parke-Davis and Dr. David Orloff.

As requested by Dr. Orloff, following you will find our complete response.

In Table 1, the mean baseline, and the median, 25th percentile, and 75th percentile of the percent changes from baseline are provided for placebo and each dose of atorvastatin. This table includes summary information for HDL-C, LDL-C, total cholesterol, and triglycerides.

Table 2 contains the adjusted mean percent change from baseline in HDL-C, LDL-C, total cholesterol, and triglycerides. The adjusted means and standard errors are based on an analysis of covariance model that includes the effects due to study, treatment, and the baseline value. Data from patients who received pravastatin 20 mg and simvastatin 10 mg were also included in fitting the model in order to be consistent with the approach used for the sNDA.

Please forward the information to Dr. Orloff. This response will also be filed to our application.

If there are any questions, do not hesitate to contact me at 734/622-1537.

Cheryl Beal Anderson, Pharm.D.
Parke-Davis Pharmaceutical Research
Manager, FDA Liaison

APPEARS THIS WAY
ON ORIGINAL

Table 1. Summary of the Baseline Mean and Percent Change from Baseline (Median, 25th Percentile, and 75th Percentile) in HDL-C, LDL-C, TC, and TG for Fredrickson Types IIa and IIb Patients Using the Atorvastatin Cumulative Integrated Database[a] (CID)

		HDL-C				LDL-C				TC				TG			
	N	BSL Mean	% Change from BSL Median	25th	75th	BSL Mean	% Change from BSL Median	25th	75th	BSL Mean	% Change from BSL Median	25th	75th	BSL Mean	% Change from BSL Median	25th	75th
Placebo	250	48.7	0.0	-6.2	8.5	197.6	1.1	-6.0	8.2	283.5	1.6	-3.9	6.6	186.1	2.6	-15.8	20.8
Atorva 10 mg	1871	47.6	6.4	-1.4	14.3	192.2	-37.7	-44.0	-29.9	276.7	-28.1	-33.2	-21.9	186.5	-20.7	-35.0	-4.4
Atorva 20 mg	147	48.0	8.7	0.0	17.1	211.7	-47.8	-51.9	-37.0	293.7	-35.0	-40.2	-27.1	170.7	-25.0	-37.7	-4.2
Atorva 40 mg	115	48.3	7.8	0.0	15.6	194.1	-48.1	-58.4	-40.9	276.6	-36.8	-44.7	-29.0	170.3	-27.1	-40.1	-11.7
Atorva 80 mg	318	45.5	5.1	-2.7	14.7	268.2	-55.2	-61.0	-47.4	346.8	-44.7	-49.9	-38.4	166.6	-34.3	-46.2	-19.7

Atorva = Atorvastatin; BSL = Baseline

[a] Data from 24 atorvastatin studies completed as of July 8, 1998.

Table 2. Adjusted[a] Mean Percent Change from Baseline in HDL-C, LDL-C, TC, and TG for Fredrickson Types IIa and IIb Patients Using the Atorvastatin Cumulative Integrated Database[b] (CID)

		HDL-C		LDL-C		TC		TG	
	N	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Placebo	250	0.2	1.0	3.5	0.9	1.9	0.7	6.6	1.9
Atorva 10 mg	1871	6.4*	0.6	-33.8*	0.6	-26.1*	0.5	-16.3*	1.2
Atorva 20 mg	147	7.8*	1.5	-39.9*	1.4	-32.1*	1.1	-21.2*	2.9
Atorva 40 mg	115	7.1*	1.4	-46.9*	1.3	-35.9*	1.0	-22.0*	2.7
Atorva 80 mg	318	5.0*	1.4	-54.2*	1.3	-42.5*	1.1	-30.2*	2.8

* significantly different from placebo, $p < 0.05$.

TC = Total Cholesterol; TG = Triglycerides; Atorva = Atorvastatin; SE= Standard error.

[a] Least squares means from ANCOVA model with study, treatment, and baseline.

[b] Data from 24 atorvastatin studies completed as of July 8, 1998.

Pharmaceutical Research
2800 Plymouth Road Phone: (734) 622-7000
Ann Arbor, MI
48105

FAXVIS

October 20, 1999

ORIGINAL

NDA 20-702
Ref. No. 097
Lipitor® (atorvastatin calcium) Tablets

NDA SUPPLEMENT
S-018-EH

Re. Amendment to Efficacy
Supplement – 018

Solomon Sobel, M.D.
Director
Division of Metabolism and Endocrine
Drug Products (HFD-510)
Document Control Room 14B-19
Center for Drug Evaluation and Research
Food and Drug Administration
Parklawn Building
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Sobel:

ehalf of, and as agent for Warner-Lamber Export, reference is made to our supplement (S-018), submitted March 3, 1999 (Ref. No. 83), to our approved NDA 20-702 for Lipitor® (atorvastatin calcium) Tablets. This supplement supports the use of atorvastatin to decrease the non HDL-C/HDL-C ratio and to increase HDL-C in patients with primary hypercholesterolemia (hetrozygous familial) and mixed dyslipidemia (Fredrickson Type IIa and Type IIb).

In accordance with 21 CFR Part 54 and 21 CFR 314.50 (k), we are herewith submitting a financial certification statement for investigators involved in studies supporting this supplemental NDA. A narrative describing our approach to compliance with 21 CFR Part 54, a signed Form 3454, and a list of investigators for whom certification is provided are attached.

Should you have any questions regarding this submission, please contact me at 734/622-5225 or send a facsimile to 734/622-3283.

/S/
12-1-99

Sincerely,

Jeffrey R. Koup

Jeffrey Koup, Pharm.D.
Director
Worldwide Regulatory Affairs

REVIEWS COMPLETED
CSO ACTION
☐ LETTER
CSO INITIALS DATE

JK:kb 10-20-1999\RN-097\20-702\CI-0981\Letter
Attachments

/S/
12/1/99

Pharmaceutical Research
2800 Plymouth Road Phone: (734) 622-7000
Ann Arbor, MI
48105

PARKE-DAVIS

March 3, 1999

NDA 20-702
Ref. No. 83
Lipitor®
(atorvastatin calcium) Tablets

Re: Efficacy Supplement

Solomon Sobel, M.D.
Director
Division of Metabolism and Endocrine
Drug Products (HFD-510)
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Attention: Document Control Room 14B-19
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Sobel:

In accordance with Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act and 21CFR 314.50, Parke-Davis is submitting a supplement to approved NDA 20-702 for Lipitor® (atorvastatin calcium) Tablets (sNDA). This sNDA supports the use of atorvastatin to decrease the non HDL-C/HDL-C ratio and to increase HDL-C in patients with primary hypercholesterolemia (hetrozygous familial) and mixed dyslipidemia (Fredrickson Type IIa and Type IIb).

As required under the FDA Modernization Act of 1997, the application fee of ( ) was sent to the Food and Drug Administration in care of Mellon Bank, Pittsburgh, Pennsylvania on February 10, 1999. The User Fee cover sheet (Item 18) is contained in Volume 1; the Identification Number for this submission is [ ].

The sNDA contains an archival copy containing 35 volumes and review copies for each technical reviewer. Only clinical efficacy data are presented in this submission; therefore, the only full technical sections are Items 8 and 10.

Patent Information (Item 13) and Debarment Certification (Item 16) are located in Volume 1 of the sNDA, immediately preceding Item 1, sNDA Index.

The data sources used to support this proposed change are identified below:

1. Summary of Adjusted Mean Percent Change From Baseline in HDL-C, Total-C/HDL-C, LDL-C/HDL-C, and Non HDL-C/HDL-C Ratios by Dose of Atorvastatin (10, 20, 40, and 80 mg), Pravastatin 20 mg, and Simvastatin 10 mg for Patients With Fredrickson Types IIa or IIb Hyperlipoproteinemia Using the Atorvastatin Cumulative Integrated Database (Data From the NDA Database [20 Studies] and Post-NDA Completed Studies 981-069, -070, -072, and -225).*

2. A Comparison of the Cost-Effectiveness of Treating to NCEP-Recommended LDL-C Concentration With Atorvastatin, Fluvastatin, Lovastatin, or Simvastatin in Patients With CHD and/or PVD (Protocol 981-69).

3. A Comparison of the Resource Efficiency of Treating to National Cholesterol Education Program (NCEP) Target LDL-C Concentrations With Atorvastatin, Fluvastatin, Lovastatin, and Simvastatin in Patients With Risk Factors for Coronary Heart Disease (CHD) (Protocol 981-070).

4. A Comparison of the Cost-Effectiveness of Treating to Modified EAS-Recommended Plasma LDL-C Concentration (<110 mg/dL) With Atorvastatin, Fluvastatin, Pravastatin, and Simvastatin in Patients With CHD and/or PVD (Protocol 981-72).

5. A Multicenter, 6-week, Randomized, Open-Label, Parallel-Arm Study Comparing the Efficacy of Once-Daily Atorvastatin With Cerivastatin in Hypercholesterolemic Patients (Protocol 981-430-225).

The sNDA is also available as an electronic regulatory submission (ERS). Items 11 (Case Report Tabulations)and 12 (Case Report Forms), and are presented only in electronic format. All other portions of the submission are presented in both electronic and paper format.

*Please note case report forms for deaths and drop-outs are only being provided for post-NDA completed studies 981-069, -070, -072, and –225 and not from the previously reviewed NDA studies.

The ERS contains images of all documents in the paper copy of the sNDA, except as listed below:

Paper Submission	**Electronic Submission**
Cover pages for each section with a table of contents will be included	Cover pages for each section with a table of contents may not be included
sNDA page numbers at top right corner of each page; individual document page numbers at top center of each page	sNDA page numbers not shown (however, ERS index shows page number of documents in paper submission, and individual document page numbers shown); hyperlinks allow navigation through sNDA
Research Report shows signature where appropriate	Research Report signature not shown

In accordance with the September 1997, " Guidance for Industry – Archiving Submissions in Electronic Format- NDAs," the electronic archive of the ERS is described in the attachment to this letter.

Should you have any questions regarding this submission, please contact me at 734/622-7425 or FAX 734/622-3283. For technical questions pertaining to the ERS please contact Mr. John Brussolo at 734/622-7156, cellular phone 734/216-1274, FAX 734/622-5152 or e-mail at **John.Brussolo@wl.com**.

Sincerely,

Byron Scott

Byron Scott, R.Ph.
Director
Worldwide Regulatory Affairs

BS/dp
03-03-1999\RN-083\20-702\CI-0981\Letter

Attachments

Desk Copy: Dr. D. Orloff, Vol. 1